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EXAMINER	
ENEWOLD, J	
ART UNIT	**PAPER NUMBER**
1655	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/137,822	Michael Naesby
Examiner	**Group Art Unit**
Jeanine Enewold	1655

☒ Responsive to communication(s) filed on *Nov 20, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-30* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. The specification is objected to because the Brief Description of the Drawings refers to Figure 1 when both Figure 1a and Figure 1b have been described. Similarly, Figure 2 is referred to in the specification, however, Figure 2a and 2b are described. This objection can be easily overcome by changing the specification to read "Figure 1a and Figure 1b" and "Figure 2a, and 2b" respectively.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2, 4, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method including the formation of a triple stranded helix region of four or more bases, does not reasonably provide enablement for forming a triple stranded helix with a triple stranded region of less than 4 bases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The claims are not commensurate in scope with the disclosure because the specification has not provided sufficient guidance to enable the

skilled artisan to make triplex bonding regions of one to three bases without undue experimentation.

The claims are broadly drawn to a nucleic acid detection method involving the formation of a triple stranded region as small as one to three bases. The specification teaches several examples which have a triple stranded region of 6 bases. However, the specification does not teach the formation of a triple stranded regions of 1-3 bases.

The art also does not support the formation of triplexes as small as 1-3 bases. Hogan (5,179,996)(January 5, 1993) taught the method for identifying nucleotide target sequences of greater than about 20 nucleotides (abstract). Further, it is taught that "the stability of the binding is dependent on the size of the oligonucleotide..." (Col 7, lines 32-42). Fresco (5,422,251)(June 6, 1995) teaches a triple stranded region "of adjacent purine nucleoside residues at least 10 nucleoside residues in length" (Col 2, 33-34). Ts'o (5,834,185) teaches a preferred target sequence for detection, recognition, and/or inhibition have from about 4 to about 40 nucleosides (Col. 6, lines 5-7).

In order for the skilled artisan to use the claimed detection the triplex must be sufficiently stable to allow its detection by conventional techniques. Oligonucleotides used as primers and probes in conventional duplex hybridization based methods are at least about 10 nucleotides to form stable complexes which can be detected.

Based upon the art and the teaching in the specification formation of a triple helix region of 1-3 bases would be unpredictable due to its expected instability. Consequently, undue

experimentation would be required of the skilled artisan to practice the invention because the artisan would be required to discover new analogs of increased binding affinity in triplexes than currently known bases in order to allow triplexes of **1-3** bases to stably form and to be detectable under assay conditions.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-21, 23-24 and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-21, 26-30 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for "determination of a nucleic acid molecule" but the final process step is determining the amount of nucleic acid A by measuring". Therefore the claims are unclear as to whether the method is a method for determination of a nucleic acid or a method of measuring nucleic acid.

B) Claims 1-30 are indefinite over the recitation "at least one molecule C". It is unclear what is meant by at least one molecule C. The claim is drawn to a triple stranded region comprising nucleic acid molecule A, nucleic acid A binding molecule B and nucleic acid binding

molecule C. The inclusion of more than one molecule C would include a fourth element which would imply a four stranded molecule.

C) Claims 2, 5, 7, 8, 26, and 27 are indefinite over the recitation "each of molecules A, B and C" because "B, and C" lacks antecedent basis.

D) Claims 7 and 8 are indefinite over the recitation of "two different molecules C" because it is unclear whether the two different C molecules are different or identical in sequence and consequently whether they bind to the same of different regions.

E) Claim 16 is indefinite over the recitation of "binding region of nucleic acid A binding molecule B to nucleic acid A consisting of pyrimidines because it is unclear whether the nucleic acid A consists of pyrimidines or whether the nucleic acid A binding molecule B consists of pyrimidines.

F) Claims 23 and 24 are indefinite over the recitation "the sequence of B is..." because "the sequence of B" lacks antecedent basis.

G) Claim 26 is indefinite over the recitation "contribute more than 1 but less than 8 bases .." because it is unclear what nucleic acid A and nucleic acid A binding molecule B and C are contributing to. Amending the claim to recite, "contribute more than 1 but less than 8 bases to the triple stranded region" would obviate the rejection.

H) Claim 30 is indefinite because the claim recites "n is an integer of at least 3, x is an integer from 2 to n-1". However, neither n nor x are defined in the claim. Further, Claim 30 is

indefinite because the claim does not include Q and I in the formula claimed but Q and I are defined. It is unclear what Q and I are referring to in the claim.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-6, 9-14, 16-19, 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o et al (5,834,185) in view of Vardimon (5,906,976).

Ts'o teaches a "method of detecting, recognizing and/or inhibiting or altering expression of a single stranded nucleic acid having a target sequence by binding Second and Third Strands which comprise oligomers...." (Col 3). Further, the "formation of triple helix complexes of single stranded nucleic acids using nucleoside oligomers which comprise pyrimidine analogs is disclosed (title). Ts'o teaches a triple helix complex termed the "closed sandwich" which is formed when the target sequence consists only of purine residues and involves the binding of a homopyrimidine oligomer as a second strand and a third strand binding to the other side (limitations of Claims 16). The second strand has a nucleoside base sequence which binds to the target sequence by Watson-Crick base pairing and the third strand hydrogen bonds to the target strand (Col. 11, lines 15-35)(limitations of Claim 12). The second and third strands do not "participate in hydrogen

bonding with each other". In this arrangement the target strand must "break away from two sets of hydrogen-bonding interactions with the oligomers", thus creating a more favorable arrangement in some situations (Col. 11, lines 54-58). The Second and Third Strands may comprise separate Oligomers from about 4 to about 40 nucleosides (Col. 16, lines 33-37)(limitations of Claims 2, 4-6, 26, 27). "The sugar moiety and backbone linkages of the oligomer probe strands can be any that are available" (Col. 15, lines 57-59)(limitations of Claim 14). "Detectably labeled oligomers may be used as proved for use in hybridization assays, for example, to detect the presence of a particular single-stranded nuclei acid sequence"(Col. 18, lines 43-46). Further the invention may be used "diagnostically to detect the presence or absence of the target DNA or RNA sequences to which the Oligomers specifically bind. Such diagnostic tests are conducted by hybridization through triple helix complex formation which is then detected by conventional means. For example, oligomers may be labeled using radioactive florescent.... Alternatively, the presence of a triple helix may be detected by antibodies which specifically recognize forms." (Col 20, lines 18-28)(limitations of Claims 13 and 21).

Although Ts'o suggests that the detectably labeled oligomers may be used in hybridization assays, Ts'o does not specifically teach determining the amount of "nucleic acid A".

However, Vardimon teaches quantification of DNA fragmentation (col 13, lines 41-59). DNA fragmentation was assayed and fractionated by electrophoresis in 1.8% agarose gels. "The gels were stained with ethidium bromide, visualized by UV light and photographed. DNA fragmentation was quantitated by densitometric scanning of the pictures" (col 13, lines 55-59).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the method of Ts'o with the teaching of Vardimon to obtain the claimed invention because Vardimon showed that by using desitometry not only was a target nucleic acid detected in a sample, but additionally was quantitated thereby improving the sensitivity, applicability and amount of information obtainable from the method of T'so.

8. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o (5,834,185) in view of Vardimon (5,906,976) as applied to Claims 1-6, 9-14, 16-19, and 21-27 above, and in further view of Corey (Trends Biotechnol., Jun 1997).

Neither Ts'o nor Vardimon specifically teaches PNA as a nucleic acid analogue in nucleic acid hybridization assays.

However, Corey teaches that Peptide nucleic acids (PNAs) are DNA analogs containing neutral amide backbone linkages. Further, PNAs are stable to degradation by enzymes and hybridize to complementary sequences with higher affinity than analogous DNA oligomers (abstract). Cory teaches PNAs are particularly useful in triple helix formation which Corey calls strand invasions (pg 227, col 1). Corey teaches that initially, PNAs were targeted to polypurine-polypyrimidine tracts. Further, Corey teaches PNA's used in triplex formation. As seen in Figure 3, possible intermediates are suggested during strand invasion of duplex DNA. In step three, the PNA oligomer completes strand invasion and high-affinity PNA hybridization discourages

reformation of duplex DNA. Additionally, Corey teaches that the absence of charge repulsion, caused by hybridization of DNA Oligonucleotides to DNA and RNA, in PNA-DNA or PNA-RNA duplexes increase the melting temperature (pg. 226, para 1).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time of the invention was made to have modified the method of Ts'o in view of Vardimon to have used the PNA oligonucleotide of Corey in order to make the claimed invention as a whole. The ordinary artisan would have been motivated to have used PNA oligomers in the triplex method of T'so because Corey teaches that the triplexes formed using PNAs are more stable than with DNA oligomers. Corey further teaches that PNA hybridization has the advantage of requiring less oligomer be added in the assay due to the higher rate of annealing. Corey also taught that the rate of recognition is increased due to the greater association constants for PNA hybridization which decreases the concentration of oligomer necessary.

9. Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o, Vardimon and Corey as applied to Claims 1-6, 9-14, 16-19, 21-27 above, and further in view of Buchardt et al (WO 92/20702).

Neither Ts'o, Vardimon nor Corey specifically teach the Formula I, II, nor III.

However, Buchardt teaches that Formulas I-II are general formulas of PNAs.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time of the invention was made to have modified the method of Ts'o in view of Vardimon and Corey to

include the use of PNAs having Formula I, II and III taught by Buchardt because Buchardt taught that these formulas represented well known PNAs thus establishing the PNAs of formula I, II, and III as species equivalent to the PNAs generically described by Corey.

10. Claims 1, 3, 5, 6, 10-13, 19, 22, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Svinarchuk (J Biol Chem 1995 Jun 9;270(23):14068-71) in view of Vardimon (5,906,976).

Svinarchuk teaches triple helix formation in which "the stability of double-stranded DNA is increased by the binding of the third strand"(abstract)(limitation of Claims 1, 22 and 25). Oligonucleotides were synthesized and labeled (Pg 14068, Col 2, Para 2)(limitation of Claim 13). The triple helix was formed and monitored by 5% polyacrylamide gel electrophoresis (Pg 14068, Col 2, Para 2)(limitations of Claim 1 and 25). The thermostability was monitored by a thermometer (Pg 14068, Col 2, Para 2). As seen in Figure 3, there is only one nucleic acid binding molecule C in the triple stranded region, nucleic acid binding molecule B is smaller than nucleic acid binding molecule C, nucleic acid binding molecule C has a length of at least 6, nucleic acid binding molecule B is capable of having either an asymmetrical or a symmetrical base sequence, nucleic acid binding molecule B is bound to nucleic acid A via Hoogsteen base pairing while nucleic acid binding molecule C is bound to nucleic acid A via Watson and Crick binding, and nucleic acid binding molecule C fully spans the region of nucleic acid binding molecule B (limitations of Claims 3, 5, 6, 10-12, and 19).

Although Svinarchuk suggests that the detectably labeled oligomers may be used in hybridization assays, Svinarchuk does not specifically teach determining the amount of "nucleic acid A".

Vardimon teaches quantification of DNA fragmentation (col 13, lines 41-59). DNA fragmentation was assayed and fractionated by electrophoresis in 1.8% agarose gels. "The gels were stained with ethidium bromide, visualized by UV light and photographed. DNA fragmentation was quantitated by densitometric scanning of the pictures" (col 13, lines 55-59).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the method of Svinarchuk with the teaching of Vardimon to obtain the claimed invention because Vardimon showed that by using desitometry not only was a target nucleic acid detected in a sample, but additionally was quantitated thereby improving the sensitivity, applicability and amount of information obtainable from the method of Svinarchuk.

11. Claims 1-3, 6, 13-14, 16, 19, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fresco (5,422,251) in view of Vardimon (5,906,976).

Fresco teaches a method of forming a triple stranded nucleic acid and method of "finding polypurine regions in double stranded nucleic acids...."(Claim 1 and 25)(abstract and Col. 14, lines 5-68). The method of identification includes digesting DNA from organism with restriction enzymes, passing DNA through sepharose column to which poly(I) strands are covalently bound,

adjusting the temperature, eluting fragments, fractionalized by standard agarose gel electrophoresis, locating polypurine bands by radioautography and sequencing (Col 14-15, lines 43-10). The addition of cations increases the stability of the triple stranded helix. The triple stranded region is stable because there is energy derived from base stacking and hydrogen bonds (Col. 6, lines 44-68). Fresco teaches that the region of adjacent purine nucleosides residues involved in the triple stranded region is at least 10 nucleosides in length (Col. 2, lines 29-33)(Claim 2). The polypurine regions of the triple stranded helix can be located by radioautography since they were labeled which shows relative amount of polynucleotides in a sample (Col. 15, lines 1-4)(limitation of claim 13). Further Frescos teaches one nucleic acid binding molecule C is involved in the triple stranded region, nucleic acid binding molecule C has a length of at least 6, bases in the binding region of nucleic acid binding molecule B to nucleic acid A consist of pyrimidines, and nucleic acid binding molecule C spans fully the region of nucleic acid binding molecule B (Figure 1)(limitations of Claims 3,6,16, and 19). Additionally, Fresco teaches "at least one nucleoside residue in the third strand is substituted with a base analog"(Claim 18)(limitation of claim 14).

Although Fresco suggests that the detectably labeled oligomers may be used in hybridization assays, Fresco does not specifically teach determining the amount of "nucleic acid A".

Vardimon teaches quantification of DNA fragmentation (col 13, lines 41-59). DNA fragmentation was assayed and fractionated by electrophoresis in 1.8% agarose gels. "The gels

were stained with ethidium bromide, visualized by UV light and photographed. DNA fragmentation was quantitated by densitometric scanning of the pictures" (col 13, lines 55-59).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the method of Fresco with the teaching of Vardimon to obtain the claimed invention because Vardimon showed that by using desitometry not only was a target nucleic acid detected in a sample, but additionally was quantitated thereby improving the sensitivity, applicability and amount of information obtainable from the method of Fresco.

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Fresco (5,422,251) and Vardimon (5,906,976) as applied to Claims 1-3, 6, 12-14, 16, 19, and 25 above, and in view of Corey (Trends Biotechnol., Jun 1997).

Neither Fresco nor Vardimon specifically teaches PNA as a nucleic acid analogue in nucleic acid hybridization assays.

Corey teaches that Peptide nucleic acids (PNAs) are DNA analogs containing neutral amide backbone linkages. Further, PNAs are stable to degradation by enzymes and hybridize to complementary sequences with higher affinity than analogous DNA oligomers (abstract). Cory teaches PNAs are particularly useful in triple helix formation which Corey calls strand invasions (pg 227, col 1). Corey teaches that initially, PNAs were targeted to polypurine-polypyrimidine tracts. Further, Corey teaches PNA's used in triplex formation. As seen in Figure 3, possible

intermediates are suggested during strand invasion of duplex DNA. In step three, the PNA oligomer completes strand invasion and high-affinity PNA hybridization discourages reformation of duplex DNA. Additionally, Corey teaches that the absence of charge repulsion, caused by hybridization of DNA Oligonucleotides to DNA and RNA, in PNA-DNA or PNA-RNA duplexes increase the melting temperature (pg. 226, para 1).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time of the invention was made to have modified the method of Fresco in view of Vardimon to have used the PNA oligonucleotide of Corey in order to make the claimed invention as a whole. The ordinary artisan would have been motivated to have used PNA oligomers in the triplex method of Fresco because Corey teaches that the triplexes formed using PNAs are more stable than with DNA oligomers. Corey further teaches that PNA hybridization has the advantage of requiring less oligomer be added in the assay due to the higher rate of annealing. Corey also taught that the rate of recognition is increased due to the greater association constants for PNA hybridization which decreases the concentration of oligomer necessary.

13. Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fresco, Vardimon and Corey as applied to the Claims 1-3, 6, 13-14, 16, 19, and 25 above, and further in view of Buchardt et al (WO 92/20702).

Neither Fresco, Vardimon nor Corey specifically teach the Formula I, II, nor III.

However, Buchardt teaches that Formulas I-II are general formulas of PNAs.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time of the invention was made to have modified the method of Fresco in view of Vardimon and Corey to include the use of PNAs having Formula I, II and III taught by Buchardt because Buchardt taught that these formulas represented well known PNAs thus establishing the PNAs of formula I, II, and III as species equivalent to the PNAs generically described by Corey.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold
September 22, 1999

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